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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/753,665	01/08/2004	Dennis A. Carson	103.014US3	8816

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EXAMINER

KRASS, FREDERICK F

ART UNIT

PAPER NUMBER

1614

DATE MAILED: 03/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/753,665	<b>Applicant(s)</b> CARSON ET AL.	
	<b>Examiner</b> Frederick F. Krass	<b>Art Unit</b> 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 13 February 2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-14 and 16-19 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-14 and 16-19 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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### **Previous Rejections**

Unless specifically maintained infra, all previous rejections are withdrawn.

New grounds of rejection follow hereinafter. Since they were not necessitated by Applicant's amendment, this action is NON-FINAL.

### **Utility Rejection: Inoperative Embodiments Recited**

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 9 and 10 are rejected under 35 U.S.C. 101 because the disclosed treatment methods are inoperative and therefore lack utility, when the etodolac compound concentration is 800 uM or higher.

The specification clearly states at p. 12, lines 3 and 4 that a concentration of 800 uM racemic etodolac cannot be achieved *in vivo*. Accordingly, values of 800 to 1000 uM, corresponding to the upper end of the ranges recited in instant claims, render the methods claimed thereby inoperative at those levels (claims 1 and 2 from which they depend specify treatment "in a mammal", *i.e.*, *in vivo*).

### **New Matter Rejection**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The term "about" in claims 9 and 10 does not appear to be supported by the instant specification as originally filed. (While the concentration ranges recited therein apparently find support in the drawings as originally filed, the term "about" does not).

### **Obviousness Rejection**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

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Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8, 11-14 and 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rephaeli (USP 5,939,455) in view of WO 98/09603.

The primary reference discloses the use of beta-oxidation inhibitors, e.g., etodolac and other NSAIDS (col. 4, line 24), as potentiating agents for certain butyric acid derivative chemotherapeutic drugs. Administration is preferably oral: see col. 16,

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lines 5 et seq. Specific cancers include leukemias (col. 5, lines 31-33).<sup>1</sup> The use of such additional agents, i.e. butyric acid derivatives, is within the scope of the instant claims due to their use of the open-ended transitional phrase “comprising”. The primary reference thus differs substantively from the instant claims insofar as it does not specifically disclose a specific dosage range, e.g., 50-5000mg, or more particularly 100 to 2500mg. (It also differs from certain claims, e.g. claims 1, 18 and 19, insofar as it does not specify the use of the (-) enantiomer).<sup>2</sup> The prior art does, however, clearly teach that the dosages used will vary according to many factors, including the particular route of administration, nature and extent of symptoms, etc., across the wide range of 0.1mg to 10g per unit dose (col. 15, lines 52-67).

The secondary reference teaches that R(-) isomers of NSAIDS, including etodolac, are useful chemopreventive agents which have lower toxicities and side effects than their corresponding S isomers. See p. 7, lines 17-30 and p. 9, line 35. The prior art specifies that the “chemoprotective effect” results from a reduction in cancer cell proliferation (p. 7, lines 31 and 32). Useful dosages (which may be single or divided) range widely from 0.1 to 2000mg, and the magnitude of the dose will vary with the

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<sup>1</sup> The patent discloses the treatment of “leukemias, such as acute promyelocytic leukemia, acute myeloid leukemia, [and] acute myelomonocytic leukemia.” (Col. 5, lines 31-33). It does not specifically, *ipssisima verba*, disclose the treatment of chronic lymphocytic leukemia as recited by instant claims 10 and 11. The specific disclosure of three of the four main types of leukemia, coupled with the modifier “such as”, however, is viewed as sufficiently specific to suggest the fourth major type of leukemia (chronic lymphocytic leukemia) so concretely that the skilled artisan would “immediately envisage” same from that disclosure, given the small size of that genus. As support for this assertion, see the table at the top of p. 766 of Berkow et al, “The Merck Manual of Medical Information”, Merck Research Laboratories Publishing (1997).

<sup>2</sup> The limitations of instant claim 1 that viability be reduced, and of instant claim 2 that susceptibility be increased, would appear to be met by the prior art’s specific disclosure that therapeutic effects include induction of differentiation and reduction of proliferation, respectively, at col. 10, lines 23-30.

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severity of the condition to be treated, individual patient response, etc. (page 11, lines 26-33). The secondary reference differs from the instant claims insofar as, although it suggests the "treatment" of "neoplastic disease" generally (p. 7, line 19), it does not specifically disclose leukemia.

It would have been obvious to have used the R enantiomer of etodolac in the treatments of the primary reference, motivated by the desire to minimize toxicity and side effects as taught by the secondary reference. The selection of an appropriate dosage would be a matter of routine experimentation, as taught by both references, and thus it would have been obvious to arrived at the particular dosages recited instantly where same would be expected to provide optimal results for a particular patient.

Applicant will note that claims 9 and 10 are not subject to this ground of rejection. The prior art does not fairly suggest, teach or disclose those high plasma levels, which are far greater than levels previously used with etodolac (see, *e.g.*, the instant specification at p. 4, lines 26 and 27). Furthermore, Applicant has demonstrated that when used at such high levels, etodolac actively – and completely unexpectedly - kills leukemia cells, rather than merely exerting a chemoprotective effect. See, *e.g.*, the instant specification at p. 12, lines 11-13.

**Provisional Obviousness-Type Double Patenting Rejection (Previous)**

Claims 1-20 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 10 and 12-23 of copending Application No. 10/682,790 in view of Spiegelman et al (USP 6,552,055).

Applicant has requested that, pursuant to MPEP § 804, the instant case be allowed because the provisional nonstatutory obviousness-type double patenting rejection is the only rejection remaining in this (earlier filed) application. (Remarks, p. 6, ¶2). As is self-evident from the new grounds of rejection set forth in this Office action, that argument is now moot. Accordingly, the rejection is maintained.

**Provisional Obviousness-Type Double Patenting Rejection (New)**

Claims 1-14 and 16-19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 11-14, 26-29, 34 and 35 of copending Application No. 09/589,476, taken in view of Berkow et al ("The Merck Manual of Medical Information", pp. 765-66 and 779-80).

Both applications are drawn to methods of using etodolac compounds to treat hematopoietic cancers, differing substantively only insofar as the specific cancer recited



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by the instant application is leukemia, while the claims of the conflicting application are drawn to the treatment of multiple myeloma.

The conflicting claims more specifically recite the treatment of multiple myeloma by administering etodolac compounds in amounts "effective to kill cancerous bone marrow cells" (see specifically the last line of conflicting claim 1). As is well-known in the art as verified by the secondary reference, leukemia and multiple myeloma share the same common source, namely both arise from abnormal bone marrow cells.

Accordingly, it would have been obvious to have used the treatment methods of the conflicting claims to treat leukemia, since a treatment killing abnormal bone marrow cells would plainly be effective in treating leukemia as well as multiple myeloma, as one skilled in the art would clearly expect (as illustrated by the secondary reference).

### **Correspondence**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frederick F. Krass whose telephone number is 571-272-0580. The examiner's schedule is 9:30AM – 6:00PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

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published applications may be obtained from either Private PAIR or Public PAIR.

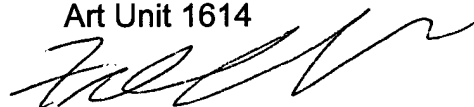
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you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free).

Frederick Krass  
Primary Examiner  
Art Unit 1614

A handwritten signature in black ink, appearing to read 'Frederick Krass', is written over the printed name and title.